September 22, 2006

David Faxon, M.D.
Maryland Health Care Commission
4160 Patterson Avenue
Baltimore, MD 21215

Dear Dr. Faxon:

I reviewed the revised proposal for the CPORT II study from Dr. Aversano.

I believe that the concept of the study is an important question that will have a major impact on patient care in Maryland community hospitals similar to the original CPORT trial regarding primary angioplasty.

The revised proposal appears to satisfy the scientific concerns expressed by the commission in the past. Each specific concern, especially regarding primary endpoints and expected event rates were addressed. I am satisfied that the revision of the primary and composite endpoints and that the expected event rates will be sufficient to answer the noninferiority trial.

The randomization question is answered within the reality of the patient's self selected presentation and probably cannot be manipulated any further.

The estimates for preprocedure stratification are based on established registries as noted and the assumptions appear valid.

We all recognize crossovers are inevitable. I agree, as a local health care provider, that we have the motivation and the patient loyalty to accentuate compliance with the trial and this would minimize crossover.

The core lab sample size was adequately justified and the consent issues were addressed appropriately.
(Continued on page 2)

The data gathering mechanisms worked well in the original CPORT trial and the additional processes should be sufficient.

The study motivation issue can be contentious. However, I agree and have experienced the overall improvement in cardiac services in our community hospital since the advent of primary angioplasty. The additional lab volume will only increase lab expertise and efficiency and will result in additional improved care.

I support the revised protocol and look forward to the results. This study should certainly aid in future policy decisions.

Thank you for your consideration.

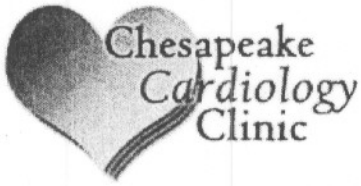
Sincerely,

Dennis C. Friedman, M.D., F.A.C.C.
Medical Director of Cardiology
Shady Grove Adventist Hospital

Cardiac Associates, P.C.
15225 Shady Grove Road, Suite 201
Rockville, MD 20850

df:bb

From: Melissa Garman [mgarman@chesapeakecardiology.com]
Sent: Monday, September 18, 2006 9:44 AM
To: Dolores Sands
Subject: CPORT II study



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Scott Friedman, M.D.
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David Faxon, M.D.
Vice-Chair, Department of Medicine
Brigham and Women's Hospital
1620 Tremont St
Boston, MA 02120

Dear Dr Faxon:

Thank you for giving me the opportunity to contribute to this panel on the topic of the CPORT II study proposed by Dr Thomas Aversano, a randomized trial on non primary PCI performed in SOS and non SOS hospitals. The mortality rate and emergency surgery rate of PCI as currently performed is quite low. Surgery on site is not usually surgery immediately available. Use of PCI in non SOS hospitals without good randomized data on this subject is increasing. The study is clearly timely. Non SOS hospitals can build more robust primary PCI programs and improve access to care, possibly reducing mortality if non inferiority exists with non primary PCI.

We are asked to review study design to assess whether the committee concerns are addressed. Dr. Cowdrey asks us not to address funding, but to leave this issue to the commission.

The selection process for patients reflects truly the question being addressed, the patients already presenting to non SOS hospitals, and requires no revisions. The study population and the

population of interest are the same.

The 3:1 randomization is key to maintaining a volume at the non SOS hospitals required to ensure quality. The sample size is large enough to allow stratification into acute and non acute coronary syndromes, and the validity of this randomization with stratification can be reviewed post hoc as done in other trials, and will be critical to perform.

The angiographic subset seems appropriate in size compared to other trials.

It is critical that any hospital or physician conflict of interest be outlined to the patient in the informed consent, and this appears to be included.

The power of the study is aided by evaluation of MACE at 9 months which is certainly mandatory. Although the mortality data can not be as "robust" standing alone as preferred by some on the committee, this is truly not possible in a randomized trial with such a low expected mortality rate involving an invasive procedure where recruitment cannot meet the expectations found in a drug trial. **This does not seem to me to be sufficient grounds to not obtain critical data.** As with all other clinical trials, this will likely answer some questions, and raise others. We can look at the results critically and then opine the statistical significance. It is my belief that Dr Aversano and the CPORT group have set up the study conditions to make this possible.

My concern about the trial is more practical in terms of recruitment of hospitals, physicians and patients, given the complex dynamics of the interventional environment. Many times these are the same interventionalists who have to work at more sites to provide the service to non SOS hospitals. I would like to know how recruitment is going now in other states, and whether any problems are occurring that may affect the achievement of the planned sample size.

In terms of your concerns at the meeting last year, it is important that you realize that the CPORT hospitals in Maryland are not a random walk through the community, but rather that the protocol requires strict adherence to training, volume, experience, back up support, and back up supporting techniques. The physicians, being the same ones who operate at the SOS hospitals, have the same approach to intervention decisions. As such, the results of such a trial must be considered in that light. I would be happy to discuss this issue with you in person if you wish.

Thank you for the opportunity to review this topic with you.

Sincerely,

Scott D Friedman, M.D. FACC

September 21, 2006

David Faxon, M.D.
Maryland Health Care Commission
4160 Patterson Avenue
Baltimore, MD 21215

RE: **C-PORT II**

Dear Dr. Faxon,

I have reviewed the material forwarded to me regarding C-PORT II. Specifically reviewed were the advised proposal, the report of the research proposal review committee, including the committee's concerns, and the C-PORTs response to those concerns.

I will not reiterate the points already made in their documents, but relay my impressions to you. First of all, I do feel there are enough social and economic benefits to perform non-primary percutaneous coronary intervention in hospitals without surgical backup to warrant a well designed study. It does appear that the complication rate of PCI is now low enough that the great majority of these procedures could be performed in such institutions with reasonable safety, but clearly a non-biased, scientific study is needed to prove this.

I believe the revised proposal is scientifically sound and feasible. I have participated in the original C-PORT Study for primary PCI at Holy Cross Hospital. I feel that study produced reliable data which had a significant impact on how patients with myocardial infarctions are treated in Maryland and probably nationally. C-PORT II is a logical extension of the original study. For many hospitals, such as Holy Cross Hospital, there are already procedures and protocols set up, not only for patient care, but also for data collection, which could be expanded to include non-primary PCI. Moreover, much of the staff of the Cardiac Catheterization Laboratory, CCU, and emergency room have a great deal of experience in these techniques. I feel the proposed study is capable of producing data which would be very helpful in guiding public policy.

Finally, I feel Dr. Aversano has adequately addressed the committee's scientific concerns. Every study has practical limitations, and must make some compromises. Dr. Aversano has explained the rationale for the study design, sample size, lack of stratification, end points, methods of statistical analysis, poor angiography sample size, and patient consensus issues. I believe that the study proposal, if carried out, would have a high likelihood of showing whether or not there is a difference in patient outcome if non-primary PCI is carried in hospitals with or without on-site surgery.

Thank you very much for asking me to comment on these issues.

Sincerely yours,

Frank N. Gravino, M.D.

FNG:cac

From: Murray, Bernadette [Bernadette.Murray@chsli.org]
Sent: Thursday, September 14, 2006 11:13 AM
To: Dolores Sands
Cc: Guerci, Alan D
Subject: CPORT-II Study

Attachments: Faxon David Letter.doc

Faxon David Letter.doc

Dear Madam,

Attached please find Dr. Guerci's letter addressed to David Faxon, MD.

<<Faxon David Letter.doc>>

If there is anything else you may need, please let us know.

Executive Assistant to
Alan D. Guerci, M.D.
President & CEO of
St. Francis Hospital

September 13, 2006

David Faxon, MD
Vice Chair, Department of Medicine
Brigham and Women's Hospital
1620 Tremont Street, OBC-3-12B
Boston, MA 02120

Dear David:

I shall be pleased to participate in a review of the revised CPORT-II Study.

As you may recall, my primary concern had to do with study power. Given the sample sizes required to detect differences in mortality smaller than 0.4 percent and the rapid proliferation of less controlled elective angioplasty around the United States, I think this is a reasonable start. I also think that the proposed funding mechanism should be adequate.

In its original review, the committee raised a number of other questions. These fall into several categories. Most could be classified as requests for clarification, and I feel that the principal investigator's responses have been satisfactory. Several more had to do with randomization. Like the principal investigator, I think that "two way" randomization is neither feasible nor necessary. With more than 18,000 patients in the study, significant imbalances

in baseline characteristics of the two study groups seems quite unlikely. I think that stratified randomization will complicate protocol compliance and, in the final analysis, create more problems than it solves. I also think that the proposed sample of 1,500 cine angiograms is sufficient. It is unlikely that this study will provide the "last word" on angioplasty without on-site surgical backup. As in the case of study power, the number of films is likely sufficient to identify major problems, whose further study can be designed and justified based on the findings of this project.

Last but not least, I think that the changes in the consent form are satisfactory.

Yours sincerely,

From: RHLEIB@aol.com

Sent: Wednesday, September 20, 2006 10:06 PM

To: Dolores Sands

Cc: richardmcalee@southernmarylandhospital.com

Subject: Revised C-Port II Proposal

Dear Dr. Faxon,

I have reviewed Dr. Aversano's revised proposal and I do believe that the updated proposal adequately addresses the concerns expressed by the panel in its review of the original proposal. I believe that the proposed research program as revised is scientifically sound and capable of producing reliable information to guide public policy.

Roy Leiboff, M.D.

From: Henry.Meilman@Medstar.Net

Sent: Thursday, September 21, 2006 5:35 PM

To: Dolores Sands

Subject: C-PORT comments for Dr. Faxon

Re C-PORT II study:
It is Unlikely the study will:
1) achieve a clinically significant outcome
2) be meaningful in light of Dr. Wennberg's study of over 600,000 patients undergoing PCI, and
3) be supported by qualified interventionalists in the Baltimore area.

Other concerns:
1) The study does not fulfill the criteria of benificence as defined in the Belmont Report.
2) The claims of "substantial geographic and temporal distance" to justify the study are neither defined nor, with few exceptions, present in Maryland.
3) There will be a dilution of skilled staff and operators over time negatively impacting the volume-quality relationship at the centers of excellence in the area.

Henry Meilman, M.D.

David Faxon, MD
Chairman, Research Proposal Review Committee
Maryland Health Care Commission

David:

Thank you for the opportunity to review and comment upon the recent "Summary of the C-PORT response to Comments of the Research Proposal Review Committee." In preparation for my comments, I have reviewed 1) Your letter to me, 2) The Committee's previous review, 3) The C-PORT response, and 4) The revised proposal.

After the Research Proposal Review Committee's learned and exhaustive review of the initial C-PORT proposal, many questions were raised about both the scientific merit and economic feasibility of the study. The Committee produced a long list of its concerns categorized broadly : 1) Study design, 2) Study structure, 3) Sample size, and 4) Funding. Within each of these broad categories were included a number of legitimate suggestions for improvement that would likely improve the opportunity for the study to produce meaningful data to guide future clinical practice and health policy.

After reading the C-PORT response and the revised protocol, I understand the changes made to include 1) 6-week followup will be extended to 9-months, and 2) The consent form has been altered to acknowledge potential financial gains of both participating hospitals and physicians.

I believe that the C-PORT response represents more of a rebuttal to the Committee's comments rather than an effort to respond to the issues raised with substantive change. As a member of the committee and as a clinical researcher, I remain concerned about significant underestimation of necessary sample size--an issue for which the C-PORT investigators seem unyielding.

Funding was a major concern of the Committee, and little progress has been made in this area. The Committee expressed its fears that the budget was profoundly underestimated (perhaps by an order of magnitude), and no progress seems to have been made in this area since the initial proposal. This same group of investigators achieved only 18% of their required sample size in their original study in large part because of budgetary problems.

In summary, I believe the revised proposal falls far short of our Committee's request for changes in the original proposal. Almost nothing has been altered to alleviate the scientific and statistical concerns of our panel, and truly nothing has been done to procure funding to assure the sound financial viability of the study. The likelihood of producing reliable and meaningful data is not much different than it was when the initial proposal was reviewed.

Thank you for the opportunity to express my views. I look forward to working with you in the future in this vital task. If I can answer any further questions regarding my position, please do not hesitate to contact me.

Mark G. Midei, MD FACC

HARVARD MEDICAL SCHOOL
Department of Health Care Policy

HARVARD SCHOOL OF PUBLIC HEALTH
Department of Biostatistics

Sharon-Lise T. Normand, Ph.D.
Professor of Health Care Policy (Biostatistics)

September 22, 2006

David Faxon
Vice-Chair, Department of Medicine
Brigham and Women's Hospital
1620 Tremont Street, OBC-3-12B
Boston MA 02120

RE: Revision of the CPORT-II Multi-State Non-Primary Angioplasty Study

Dear Dr. Faxon,

This letter is in response to your request that I review Dr. Aversano's revised proposal. In the spirit of full disclosure, I was part of a committee that unanimously advised the Massachusetts' Department of Public Health to reject an even earlier version of Dr. Aversano's proposal. The state agreed with the committee and chose to design its own study to evaluate the very important topic raised by Dr. Aversano. I serve as the senior statistical investigator on this MA study to examine this question. The MA study (referred to as MassCOMM) began to enroll patients in July of this year. The issues I raised in review of the Maryland proposal were very similar to those I raised when Dr. Aversano came to MA. While I don't believe I am bringing any biases to this review, I thought it important to make you and the Maryland Health Care Commission aware of these facts.

You raised two specific questions and I have provided my thoughts below.

1. **Does Dr. Aversano's revised proposal satisfactorily address the scientific concerns expressed in the panel's review of the original proposal?** Dr. Aversona has been very responsive to the Committee's concerns and his new proposal is much stronger. I do raise some specific issues that need clarification and one major issue that must be addressed.
    a. MINOR: Page 5 of Summary of Responses - while it may be true that it would be difficult to randomize patients who present to sites with on-site cardiac surgery, the spirit of the Committee's comments was to appropriately characterize the population to which the study findings apply. The proposed study involves a one-way randomization and the conclusions from such a study need (and must) be presented in the context of the study

Sharon-Lise T. Normand, Ph.D.
Professor of Health Care Policy (Biostatistics)

population. A careful analysis would characterize the difference between the study population of patients presenting to hospitals without SOS and the population of patients presenting to hospitals with SOS.

b. MINOR: Page 9 of Summary of Responses - the Committee surely did not imply that "anything other than a 100% sample cannot be used to assess the 'caliber, completeness, durability, etc". I am not following the statement that "increasing the sample size would not sufficiently impact accuracy of the readings of the lab results". Therefore the response to this issue is insufficient.

c. MAJOR: Page 12 of Summary Responses (Sample Size) - I am concerned about any investigator who embarks on a study assuming retention rates of 100%. This is both naïve and not good trial practice.

2. **Is the proposed research program now scientifically sound and capable of producing reliable information to guide public policy**? There are several issues to consider when answering this question. I believe Dr. Aversano's study is now scientifically acceptable and could provide very important results. In general, his responses are thoughtful. However, there are two other key considerations. The Committee raised issues of funding which clearly impact the answer to your question and which you have advised us not to comment upon in this report. The last issue is the track record and follow-through expertise of Dr. Aversano and his team (e.g., typically one would review how many trials the PI has conducted, publication records, and things of this sort in an NIH review). I am not in a position to judge this as I do not have the relevant information. This last remark is not meant as a criticism; rather it is meant to emphasize the range of information that I need to answer your question. As such, I do not have sufficient information to answer your question. I feel the science has improved and is sufficient.

I hope this information is helpful.

Respectfully,

Sharon-Lise Normand

September 20, 2006

Dear Dr. Faxon:

Enclosed please find my response to your letter of August 24, 2006.

I have had the opportunity to review the revised proposal for the CPORT-II study, as well as the panel's previous review and a summary of both the panel's concerns about the original proposal and Dr. Aversano's response to these concerns.

In my opinion, I believe that Dr. Aversano's revised proposal does address scientific concerns expressed in the panel's review of the original proposal.

It is my opinion that the proposed study, as revised, is scientifically sound and capable of producing reliable information to guide public policy.

Enclosed please find my comments regarding one specific area, "Patient Population and Randomization".

I feel compelled to specifically address this issue. The question proposed by the panel was regarding the difference between access to care and convenience of care.

I believe this is an important distinction which is frequently misunderstood and/or overlooked. A frequently cited statistic is that approximately 80% of the adult population of the United States lives within a sixty minute commute from a PCI center. (#1) While clearly this would suggest availability of angioplasty services, it does not equate to access. In fact, most patients presenting with STEMI present to hospitals without onsite surgical services. If catheter-based reperfusion strategies are employed, this then necessitates transfer to another facility. This culminates in a delay in TIMELY performance of reperfusion (and therefore access to optimal outcomes from primary PCI). A number of studies have revealed that primary PCI for STEMI can safely be performed at hospitals without onsite open heart surgery and result in outcomes better than thrombolytic therapy (#2) and similar to outcomes achieved with PCI at hospitals with onsite open heart surgery being achieved. (#3)

Subsequent studies documented that non-primary PCI in centers without onsite open heart surgery could be performed safely with similar outcomes as tertiary centers with available open heart surgery on site. (#4)

It is important to note, that only 25-35% of all patients presenting with an acute MI have new ST segment elevation or new left bundle branch block, while the remaining 65-75% do not and fall into the category of "NSTEMI". This classification of STEMI versus NSTEMI has been based on surface ECG findings (technology over 100 years old) and ignores the fact that the pathophysiology is identical (inflammatory atherothrombosis). In fact, current data derived from the Crusade registry revealed that the mortality rate in patients with NSTEMI is higher than in patients presenting with STEMI.

While "STEMI"s have clearly been shown to benefit with immediate reperfusion, the immediate reperfusion of NSTEMI and its effect on outcomes in these patients, has not been documented. While "early invasive and conservative strategies" have been debated and evaluated in the literature, no study has focused on the impact of immediate reperfusion as has been the strategy in STEMI. Dr. Aversano's current proposal would make PCI available to this NSTEMI population 24 hours a day, 365 days a year and would help address this critical clinical question.

Finally, my hospital has been performing primary angioplasty for acute MI in patients with new ST segment elevation and new left bundle branch blocks since 1996. The availability of this intervention has proven to be lifesaving in a multitude of patients who were too ill or who would not have survived even immediate transfer to tertiary centers with onsite open heart surgery.

Sincerely,

Stephen J. Plantholt, M.D.
Director of Division of Cardiology
St. Agnes Healthcare

SJP:tkg

References:

1. CIRC 2006; 113: 1189-95
2. JAMA 2002; 287: 1943-51
3. JACC 2004; 43: 1943-50
4. JACC 2006; 47: 1713-21

Karen H. Rothenberg, JD, MPA
Dean
Marjorie Cook Professor of Law

410-706-2041
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UNIVERSITY OF MARYLAND
SCHOOL OF LAW

August 30, 2006

David Faxon, M.D.
Vice-Chair, Department of Medicine
Brigham and Women's Hospital
1620 Tremont Street OBC-3-12B
Boston, MA 02120

Dear Dr. Faxon:

Thank you so much for your letter of August 24, 2006 requesting my participation on the scientific review panel for the proposal for the CPORT-II study from Dr. Thomas Aversano. Unfortunately, I have too many commitments over the next few weeks as we begin our academic year. I am so sorry I will have to decline participating in the review process at this time. I hope I can be of service in the future.

Sincerely,

Karen H. Rothenberg, J.D., M.P.A.
Dean
Marjorie Cook Professor of Law

KHR/tr

September 22, 2006

David Faxon, MD
Chairman, Research Proposal Review Committee
Maryland Health Care Commission
4160 Patterson Avenue
Baltimore, MD 21215

Q-1 Does Dr. Aversano's revised proposal address the scientific concerns expressed in the panel's review of the original proposal?

- Although the revised protocol satisfactorily addresses the main objection expressed in the original proposal (i.e., death alone could not be the sole primary endpoint), by the addition of MACE at 6wks, 3,6,&9 mos, this proposal still leaves important questions of study design unanswered. Chief among these are:

    1) **Completeness of revascularization** not adequately assessed nor clearly defined. The very wording on page 7- last para "…. any and all coronary stenoses that require treatment can be treated…" immediately indicates there will be considerable variation in the interpretation of what lesions "require treatment"; eg., operators will vary on which total obstructions require treatment and which do not; similarly, which graft lesions should be attempted and which not, etc.

    2) **Physician Selection Bias** is common in the real world of practice with "cherry-picking" of the "attractive lesion "remaining in the Community and the "ugly lesion" referred to the SOS hospital. This same tendency is certain to persist and can readily be gamed in this randomized trial since operator judgment is all that determines what is a treatable lesion. The 3:1 randomization scheme also will make it more difficult to ascertain "gaming" as will the fact that patients judged "not suitable for Rx at the no SOS hospitals" will only be included in a "limited data" registry with no angiograms evaluated at the Core lab by independent and blinded participants.

3) **Adequacy of sufficient #s of personnel to complete the workscope of the project.** As pointed out in the Report of the Review Committee on pg 9-para 2, it is difficult and time consuming to collect data on patients once they leave the hospital. It is to be noted that virtually all the secondary endpoints of the original proposal have now become primary endpoints of the study and their data acquisition takes on an entirely new dimension of completeness, accuracy, verification, etc. that must be ascertained at 6wks, 3, 6 and 9 mos. This clearly adds to the workload and expense. Consider for example verifying the occurrence of MI as a component of MACE, an important and not infrequent occurrence in this study population, for the estimated minimum 200 patients /site/yr. All hospitalizations, not just those relating to chest pain, will have to be reviewed to be certain that an admission for a GI complaint, pneumonia, gall bladder disease, etc. was not an MI. The new proposal does not indicate how this substantial increase in workload and expense is to be handled let alone acknowledge its impact on study planning.

   The investigators have not described in adequate detail the responsibilities of the DCC and its interaction with the CCC. More detail regarding interactions with other cores (EQOL Coordinating Center and Angiography Core Laboratory would also be helpful in understanding that there are adequate personnel to support these functions

4) Similar to the original proposal, there is again a failure to provide evidence that the electronic data management system has a performance record that is up to the very substantial load that it will regularly handle- without fail- in its data acquiring, monitoring and editing functions. What back-up systems, if any, are in place when the system is down? In brief, the role of the Sextant Data Monitoring System is so crucial to this study that due diligence obliges any review body to have verifiable data from an independent source that it is up to the task.

Q-2 Is the proposed research program now scientifically sound and capable of producing reliable information to guide public policy?

- Dr. Aversano provides thoughtful responses to the original critique and the "science" of the resubmission is generally restored to acceptable levels by the incorporation of the additional primary endpoint (MACE) to provide the required elements of *effectiveness, durability and quality* of PCI at non-SOS hospitals in addition to death as a non-inferiority measure. However, I must seriously question how sound and capable of producing reliable information to guide public policy" the resubmission is for several reasons:

  a) Eighteen thousand three hundred sixty (18,360) patients distributed over 40 participating sites each providing $52,000 per year per site provides $4.3 to $6.0 million dollars for the entire study. The additional endpoints (MACE) plus

bleeding, plus congestive heart failure, plus anginal levels to be assessed at 6 weeks, 3, 6 and 9 months add a major workload to a personnel staff that remains unchanged from the much simpler original proposal. Additionally, it will prove to be far more expensive than the original proposal yet the amount of funding is to remain unchanged. Failure of the investigators to account for this added expense is totally unrealistic and represents unsound practice.

b) There is no formal or informal discussion of how these limited funds will be apportioned to support the activities required of the DCC, CCC, angiographic core or the individual sites that must undergo specific training by the CCC. One must assume these component activities will be funded "from their own existing budgets" which is anything but a sound operating principle.

c) The resubmission is based on the premise that there will be 100% patient retention and therefore no need to allow for additional time or funds to acquire additional patients. This is very unsound planning for a clinical trial.

d) The no- SOS hospitals are the real stakeholders in this trial and would appear to have the greatest conflict of interest of all the funding sources identified by the investigators. That aside, serious consideration must be given to the fact that market forces being what they are, it is quite possible that a number of hospitals will withdraw from the study because of the economics of present day medicine. It is already apparent that interventional laboratories that were once considered very attractive profit centers have proven to be quite the opposite in many community hospitals in recent years. At the very recent European Congress of Cardiology, there was much discussion about adverse outcomes using the latest stent technologies that received wide coverage in the lay press that has already dampened some of the wild enthusiasm for PCI procedures among both physicians and patients alike. These and other forces such as the clinical findings that vigorous medical therapy may result in outcomes as favorable as those achieved by interventional technology, may alter the climate that currently is driving community hospitals to seek the capability of performing interventional procedures.

The above budgetary comments are made to reflect the unsound nature of the planned funding as much as they are made to indicate that a much higher dollar figure is required to have a realistic chance of obtaining reliable information. I am confident that the Commission will find reliable sources to make reasonable estimates for what the actual dollar figure should be.

Lastly, as in the review process of any grant proposal, the past performance of the PI and colleagues carries considerable weight. It is to be noted that in the only other trial by this group (CPORT-I), which was also solely funded by the participating institutions, the trial was discontinued because of lack of adequate funding when less than 18% of the required 2500 patients was recruited. The validity of this study was greatly compromised by such a serious shortfall in achieving the required number of study subjects.

I hope you will find these comments of some help in your deliberations.

Sincerely yours,

Thomas J. Ryan, MD
Past Chairman
Research Proposal Review Committee
Maryland Health Care Commission

TJR/lt

From: Jack Schwartz [jschwartz@oag.state.md.us]
Sent: Wednesday, September 20, 2006 11:07 AM
To: Dolores Sands
Cc: jsapsin@dhmh.state.md.us; Jane Pilliod; Suellen Wideman
Subject: Revised C-PORT Trial

Dear Ms. Sands,

These are my comments in response to the request in Dr. Faxon's letter of August 24. I have little to say, because I'm not qualified to comment on such crucial scientific matters as the adequacy of the randomization scheme, which is maintained as originally proposed despite the review panel's prior criticism; the power calculations, given the revised primary endpoints; and the angiographic sampling. What I can observe is as follows:

* The new primary endpoint of composite MACE at nine-months post-procedure strikes me as a key improvement toward sufficiently testing the hypothesized non-inferiority. Members of the review panel, however, suggested a one-year follow-up. The question, then (which of course I cannot answer), is whether the omission of relevant events that occur between nine months and one year would undermine the study's conclusions. Is nine months sufficient to capture most of the complications of interest?

* The inclusion of financial conflict of interest language in the consent document is helpful. (The exact wording should be left to IRB review and determination.) The investigator did not address other techniques for mitigating what can be expected to be a substantial risk of therapeutic misconception and consequent misunderstanding of randomization. This is not a fundamental objection at this stage, however, though the Commission may wish to offer this as a point for the IRBs to consider.

In short, my impression is that the inclusion of the new primary endpoint is a major step in the right direction. IF the key elements of the research design are scientifically sound (matters on which I lack expertise), the study would produce reliable information to guide public policy.

Jack Schwartz
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